Treatment of brain metastases in patients with driver mutations: WBRT, SRS or systemic treatment only?

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Disclosures

- None

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Graded Prognostic Assessment (GPA)
Lung (NSCL and SCLC)

PF	0	0.5	1.0	Pt. Score
Age	>60	50-60	<50	_____
KPS	<70	70-80	90-100	_____
ECM	Present		Absent	_____
#BM	>3	2-3	1	_____
			Sum Total =	_____

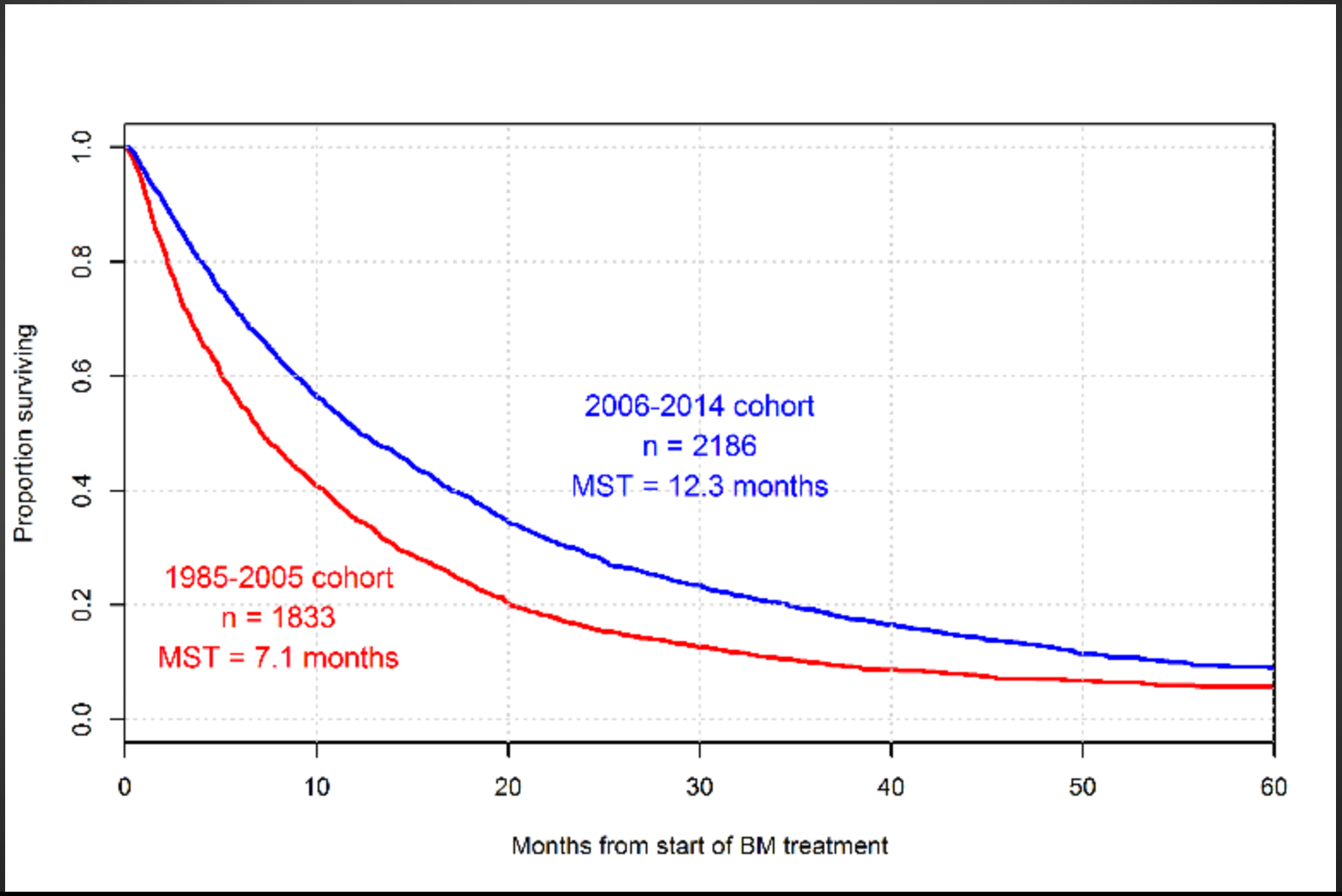
Sperduto PW et al. JCO 2012;30:419-425
www.brainmetgpa.com

Graded Prognostic Assessment

Diagnosis	Median Survival Time (months)			
GPA	0-1.0	1.5-2.0	2.5-3.0	3.5-4.0
NSCLC/SCLC	3.0	5.5	9.4	14.8
Melanoma	3.4	4.7	8.8	13.2
Breast Cancer	3.4	7.7	15.1	25.3
Renal Cell	3.3	7.3	11.3	14.8
Gastrointestinal	3.1	4.4	6.9	13.5

Sperduto PW et al. JCO 2012;30:419-425
www.brainmetgpa.com

Survival of NSCLC Patients with Brain Metastases: Comparison of Current Data to Historical Controls



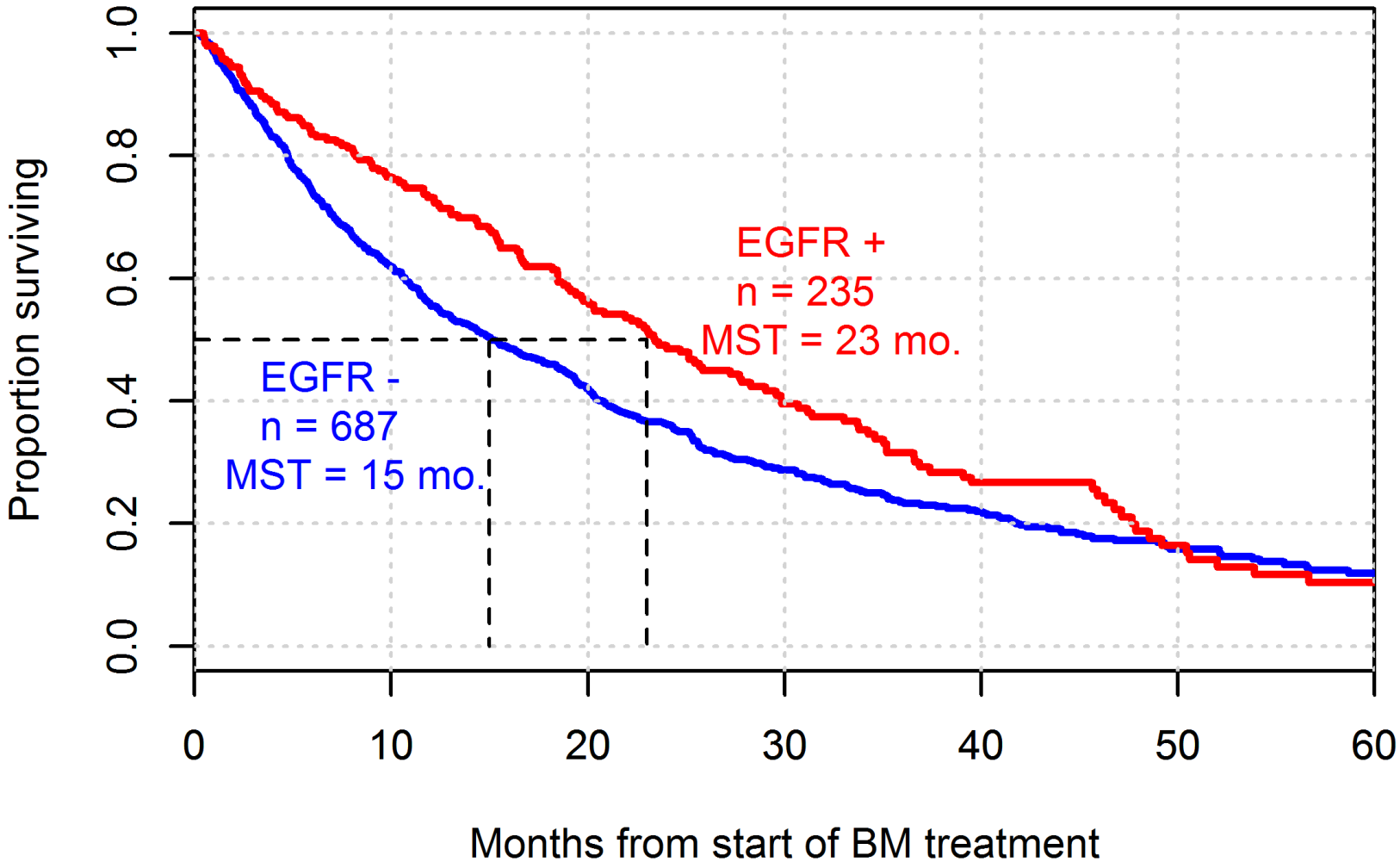
Sperduto PW et al. ASTRO 2015

Patient Population

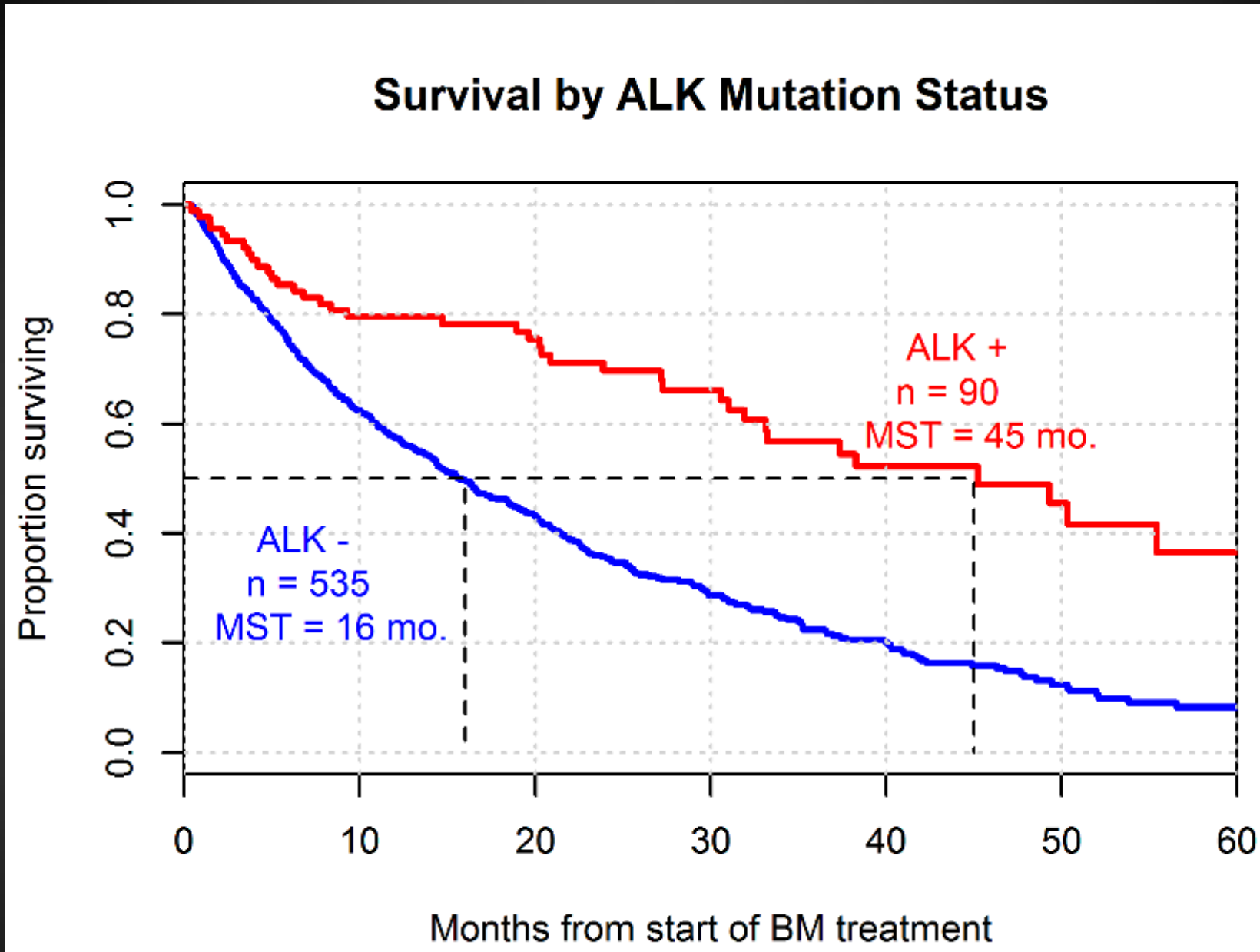
2324 patients with lung cancer
→2186 with non-small cell lung cancer
→1521 with adenocarcinoma
→993 with known mutation status

Largest reported series of gene mutations in patients with lung adenocarcinoma and brain metastases

Sperduto PW et al. ASTRO 2015

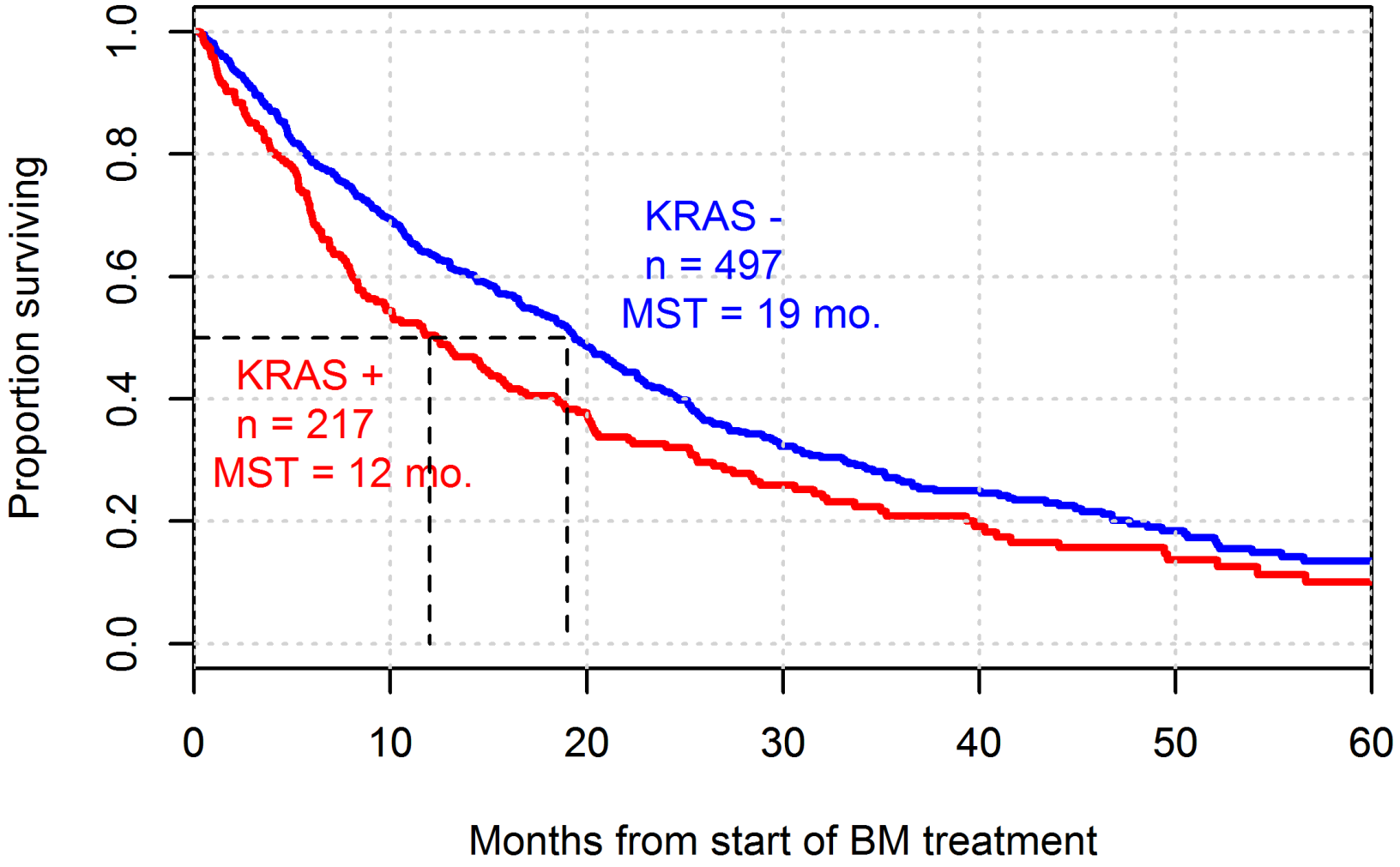


Sperduto PW et al. ASTRO 2015



Sperduto PW et al. ASTRO 2015

Survival by KRAS Mutation Status



Sperduto PW et al. ASTRO 2015

Cause of Death

In the 512 patients (34%) in which cause of death was known, 82% died from non-CNS disease, suggesting…

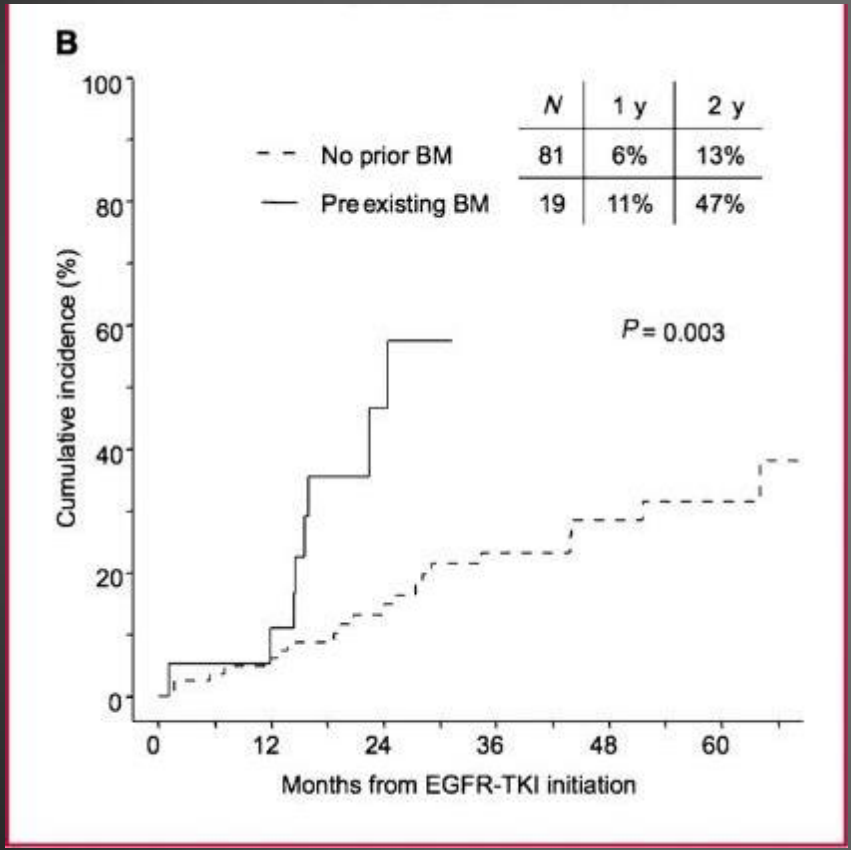
- **Systemic disease remains the primary obstacle to further progress.**
- **Local failure rate after SRS for BM is roughly 20% and those pts are likely to die from CNS progression.**

Sperduto PW et al. ASTRO 2015

Brain/LM metastases is a common site of first progression in EGFRmut and ALK+ patients

Author	Clinical Data	% Brain/LM progression	
Amuro AM, Cancer 2005	EGFRmut+/- who responded to gefitinib	33% (first site)	15m survival after dx of BM/LM
Heon S, Clin Cancer Res 2010	EGFRmut+ on gefitinib or erlotinib	29% crude; 19% at 2 years, cumulative	5-6 m survival after prog/dx of BM/LM
Shaw AT, Lancet Oncol 2011	ALK+ on crizotinib	50% cumulative	
Costa DB, J Clin Oncol 2015	ALK+ on crizotinib	20% if no prior BM, 38% if prior BM	BM responses seen. PFS similar in patients with/without BM at study entry

Cumulative incidence of CNS progression in EGFRmut+ on gefitinib or erlotinib



Increased risk of new brain metastases if prior brain metastases

Heon S et al, Clin Cancer Res 2010

NO574 SRS ± WBRT
65% NSCLC

1-3 brain mets appropriate for SRS

ECOG PS 0-2

No LM

No chemo during RT

STRATIFY

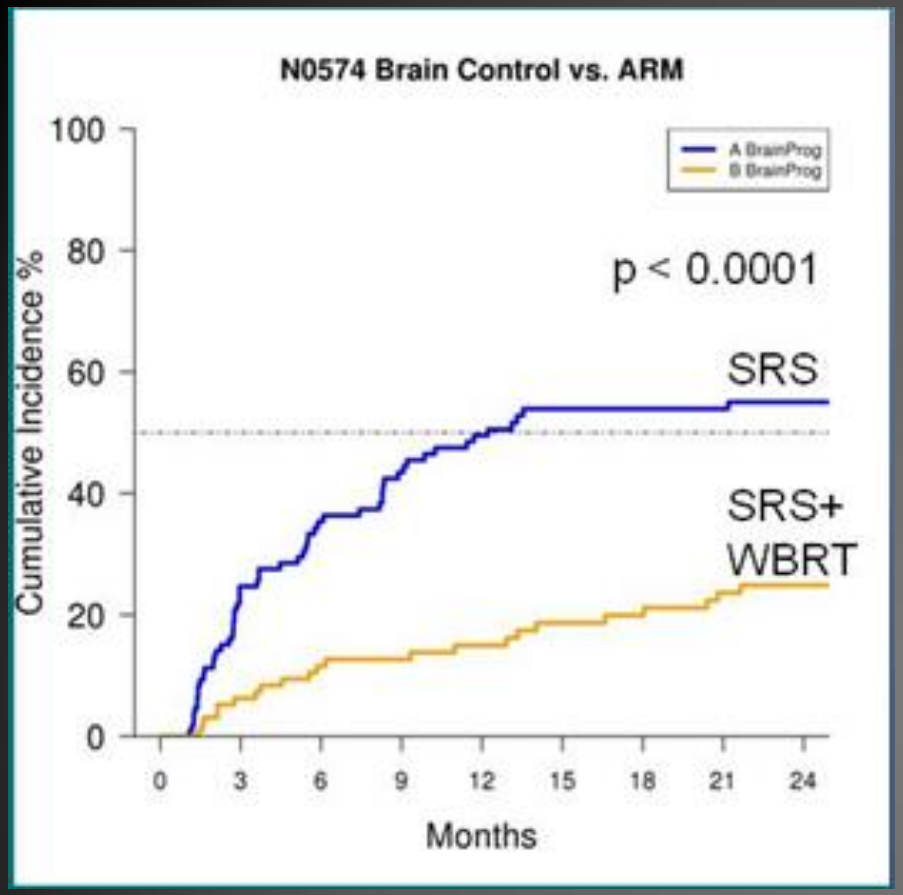
- Institution
- 1 vs 2-3 lesions
- Extracranial tumor control
- Age

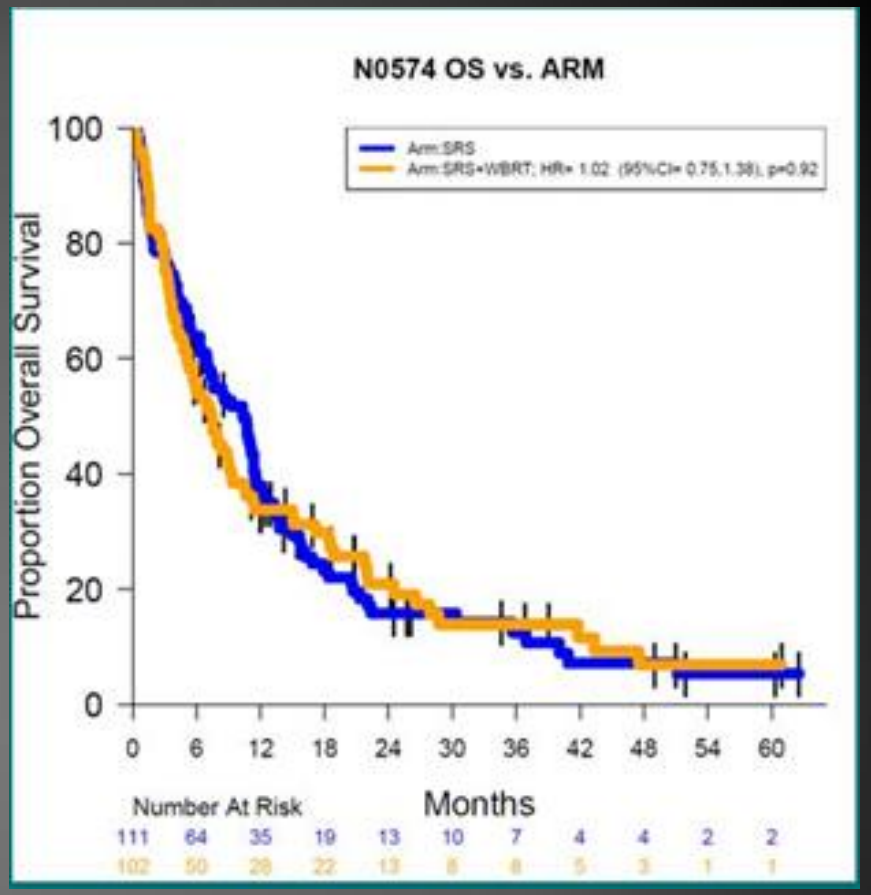
RANDOMIZE

→ SRS

→ SRS + WBRT
WBRT 30 Gy/12 fx

Primary Endpoint:	3 month neurocognitive change
Accrual:	214 patients 2002-2013





	SRS	SRS+WBRT
CNS failure @ 3 mo	24.7%	6.3%
CNS failure @ 6 mo	35.4%	11.6%

	SRS	SRS+WBRT
Median OS	10.4 mos	7.4 months

Brown P, ASCO Plenary 2015

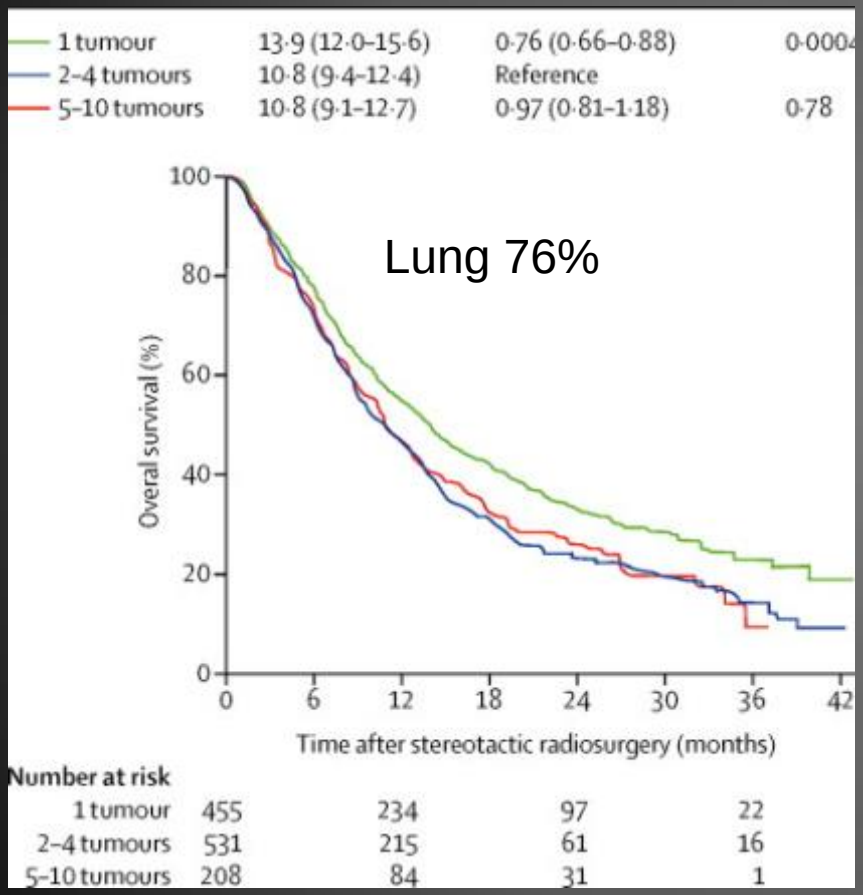
NO574 SRS ± WBRT
65% NSCLC

Neurocog Decline	SRS	SRS + WBRT	
3 months	63.5%	91.7%	p= 0.0007
6 months	77.8%	97.9%	p= 0.032

- WBRT associated with worsening
  - Neurocognition (immediate recall, memory, verbal fluency)
  - Patient-reported outcomes such as functional well-being
- But we are probably underestimating the negative impact of SRS and new brain metastases

Brown P, ASCO Plenary 2015

JLGK0901: SRS for ≤ 10 BM: Suitable alternative to SRS?



Multiviate analysis:

Poorer survival with

- More than 1 BM
- Age ≥ 65 yrs
- KPS ≤ 70
- Male gender
- Uncontrolled extracranial disease

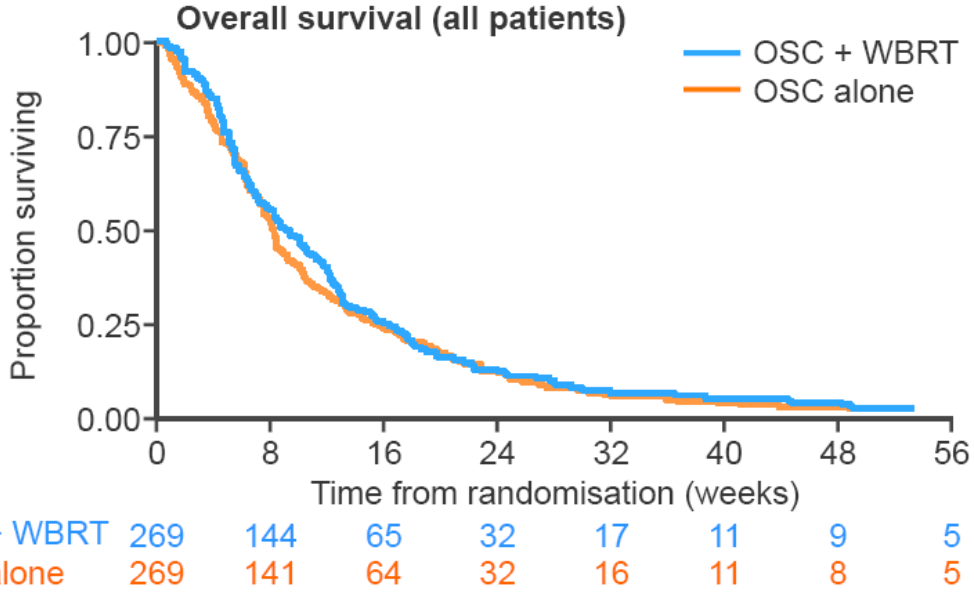
Survival not associated with

- Primary tumor type
- Cumulative tumor volume

Yamamoto M et al, Lancet 15: 387-95, 2014

WBRT of potential little value in advanced NSCLC: QUARTZ trial

- **Key results**
  - No significant difference was observed in OS between the two treatment groups



Median OS (95%CI), weeks
OSC + WBRT: 9.3 (7.4, 10.7)
OSC alone: 8.1 (7.6, 9.0)

HR (95%CI): 1.05 (0.89, 1.26)
p=0.52

  - Number of QALYs was also similar between the two treatment groups (43.3 vs. 41.4 days for OSC + WBRT and OSC alone, respectively)
- **Conclusion**
  - Whole brain radiotherapy provided no additional clinically significant benefit for patients selected for QUARTZ trial with NSCLC and brain metastases

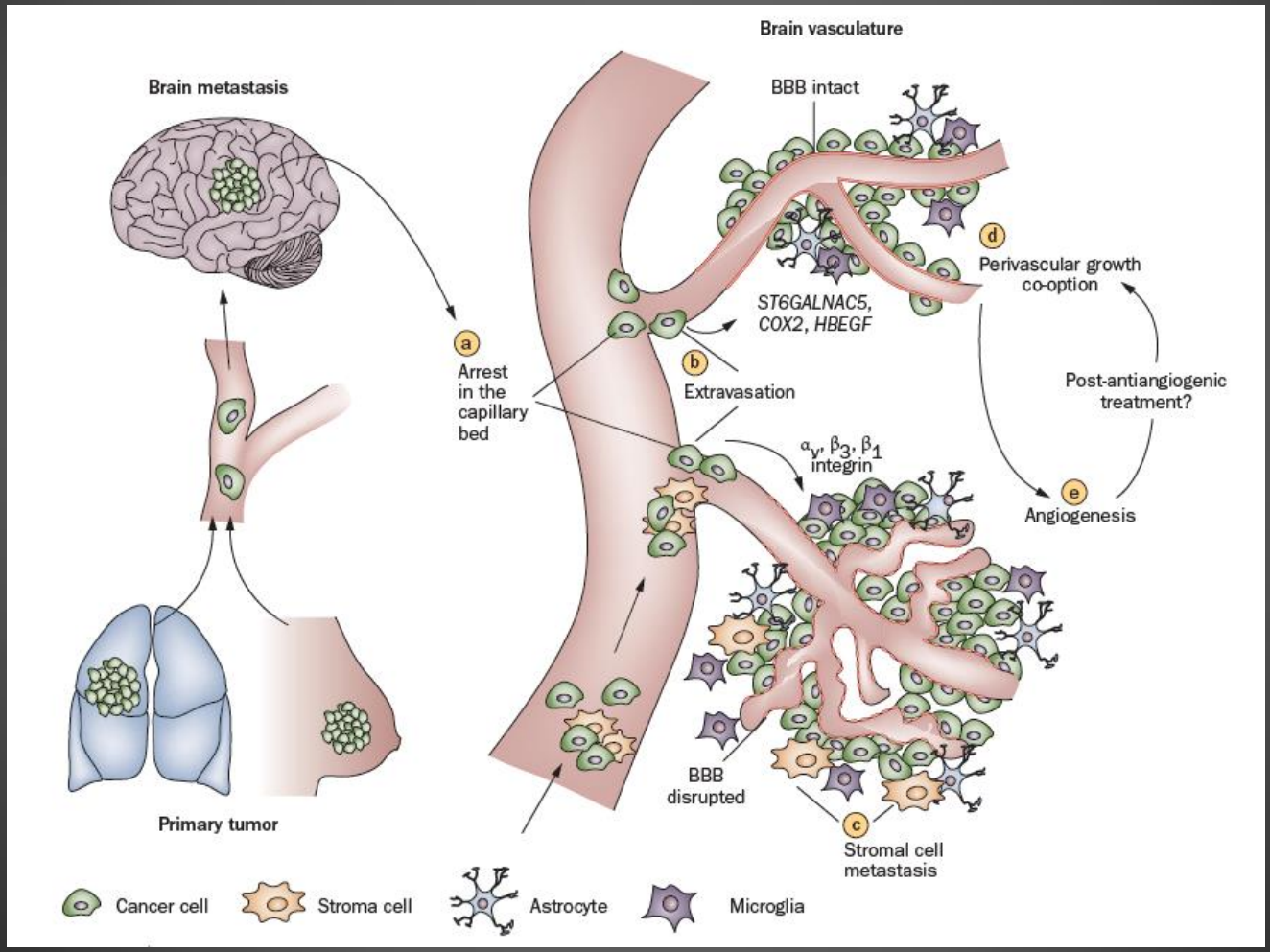
Mulvenna et al. J Clin Oncol 2015; 33 (suppl): abstr 8005

Summary so far…
NSCLC brain metastases

- SRS alone is better than SRS+WBRT in maintaining quality of life and neurocognition
- WBRT, as compared to SRS, does not improve quality of life or overall survival
- SRS suitable for up to 10 brain mets, maybe more?

For patients with targetable mutations are there better alternatives?

The biology of brain metastases formation



Eichler AF et al. Nat Rev Clin Oncol 2011

Radiation disrupts blood brain barrier

- Activation of sphyngomyelinase leads to endothelial cell damage
- Alteration of matalloproteinases, tissue inhibitors of metalloproteinases and extracellular matrix
- Disruption of BBB are seen almost immediately following radiation and may last for up to a month

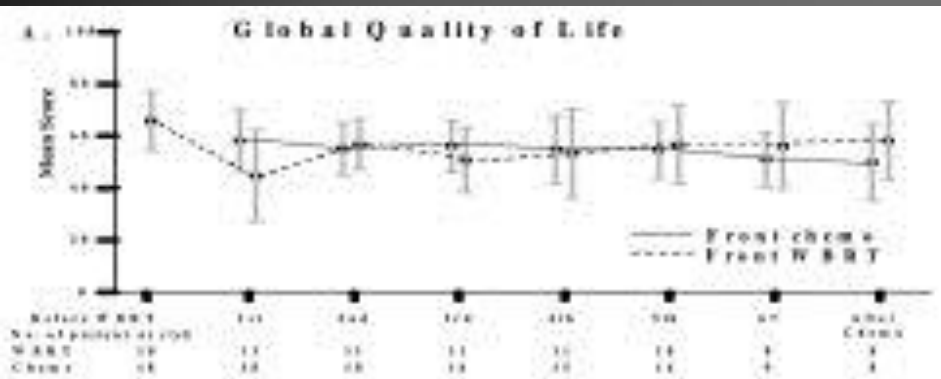
Lee WH et al, IJROBP 2012
Garcia-Barros M et al, Science 2003

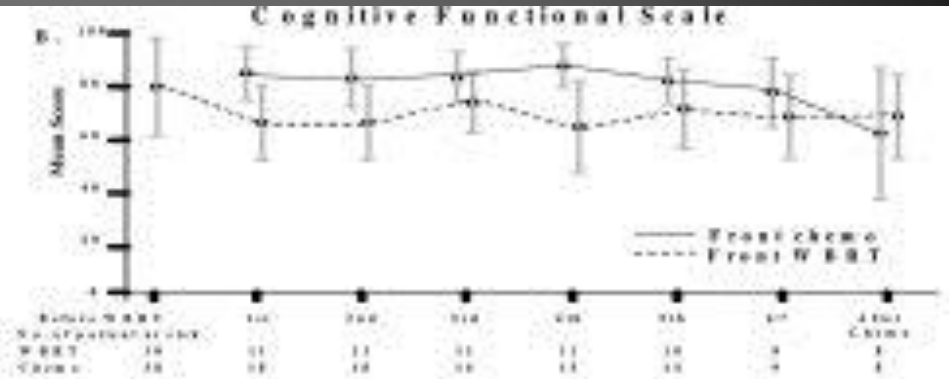
NSCL brain metastases: First line chemotherapy

Publication	Chemotherapy	ORR CNS	
Bailon O et al Neuro Oncol 2012 (n=30 adenoca)	Carboplatin Pemetrexed	40%	39 weeks OS 53% ICP
Barlesi F et al Ann Oncol 2011 (n= 43 NSCLC)	Cisplatin Pemetrexed Delayed WBRT	42%	7.4 m OS
Lee DH et al Cancer 2008 (n=48)	Gemcitabine Vinorelbine vs WBRT	39% 28%	9.1 months OS 9.9 months OS

Newly diagnosed NSCLC with synchronous brain metastases: Chemo vs WBRT

Self-reported QOL parameters (n=33)

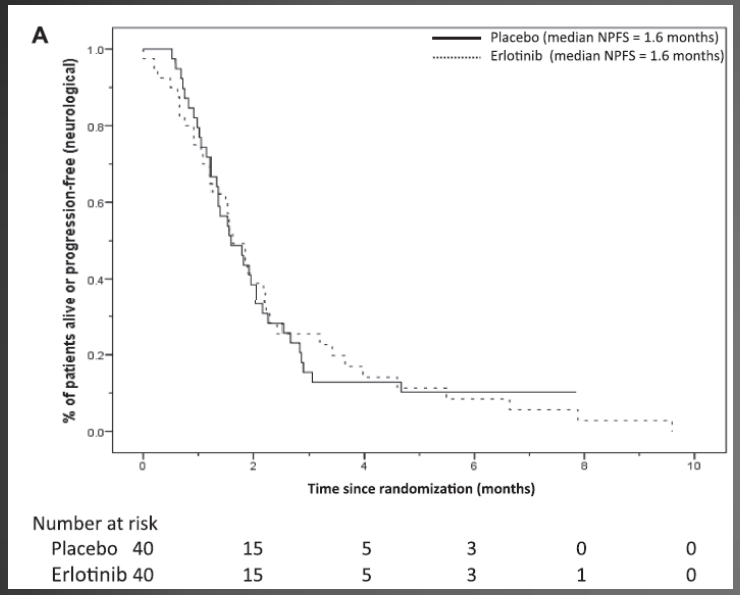




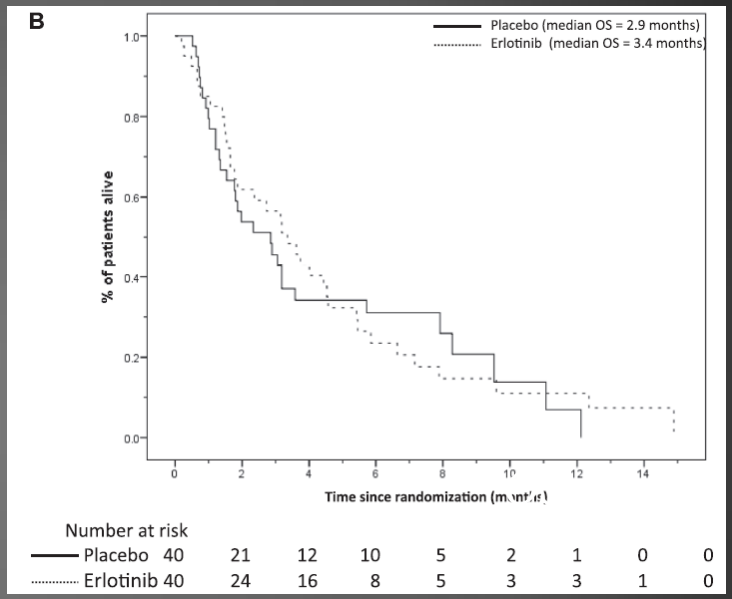
- Global health status similarly impaired in both groups
- Cognitive function impaired in both but stable for WBRT (downward trend in chemo arm?)

Lee DH et al, Cancer 2008

WBRT (20 Gy/5 fx) with Erlotinib vs Placebo: Erlotinib has little activity in unselected patients



Neurologic PFS
1.6 vs 1.6 months



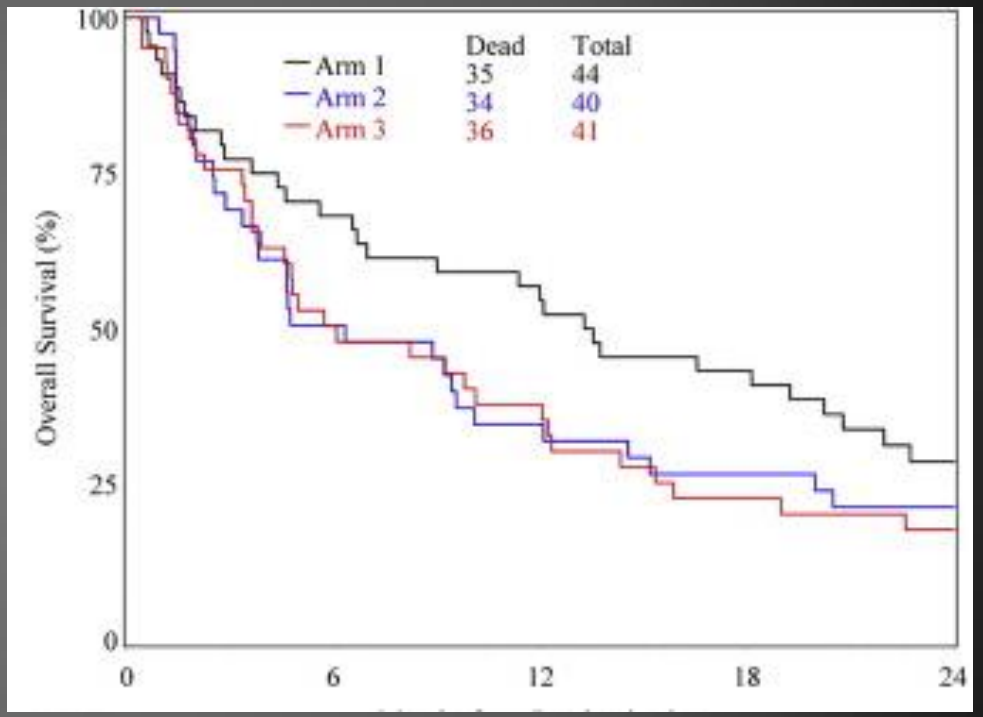
Overall survival
2.9 vs 3.4 months (NS)

- Ineligible for SRS
- No need of urgent chemotherapy
- 80% were RPA II

Lee SM et al , JNCI 2014

RTOG 0320: NSCLC Phase III
WBRT + SRS alone versus with TMZ or Erlotinib

- Closed due to poor accrual (126/381 patients)
- Median survival
  - RT alone 13 m
  - RT+ drug 6 m
- Time to CNS progression
  - Decreased in drug arms
- Toxicity
  - Increased in drug arms

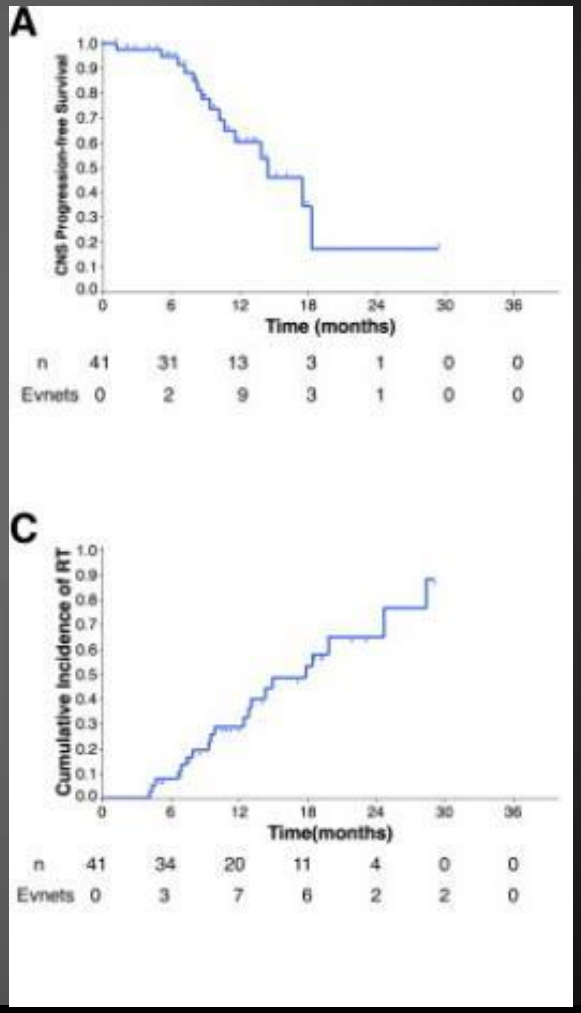


Sperduto PW et al, IJROBP 85(5):1312-18, 2012

Phase II gefitinib first for brain metastases EGFRmut+ Japanese patients (n=41)

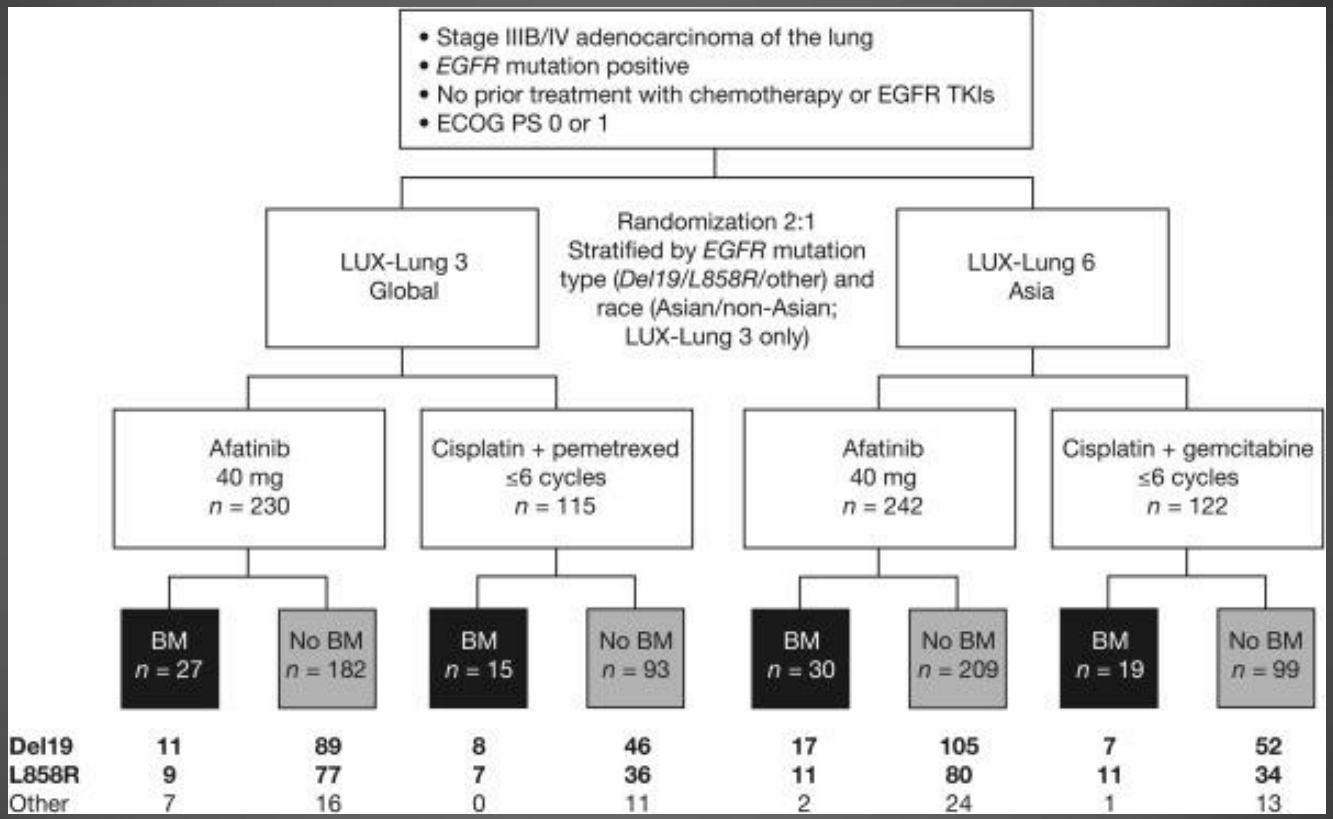
gefitinib → erlotinib → WBRT or SRS

- Median OS 22 months
- 88% response rate (CR+PR)
- Median time on gefitinib 10.6 months (intracranial progression most common)
- Cumulative “incidence of RT” near 100%, median delay of 17 months)



Iuchi T et al, Lung Cancer 2013

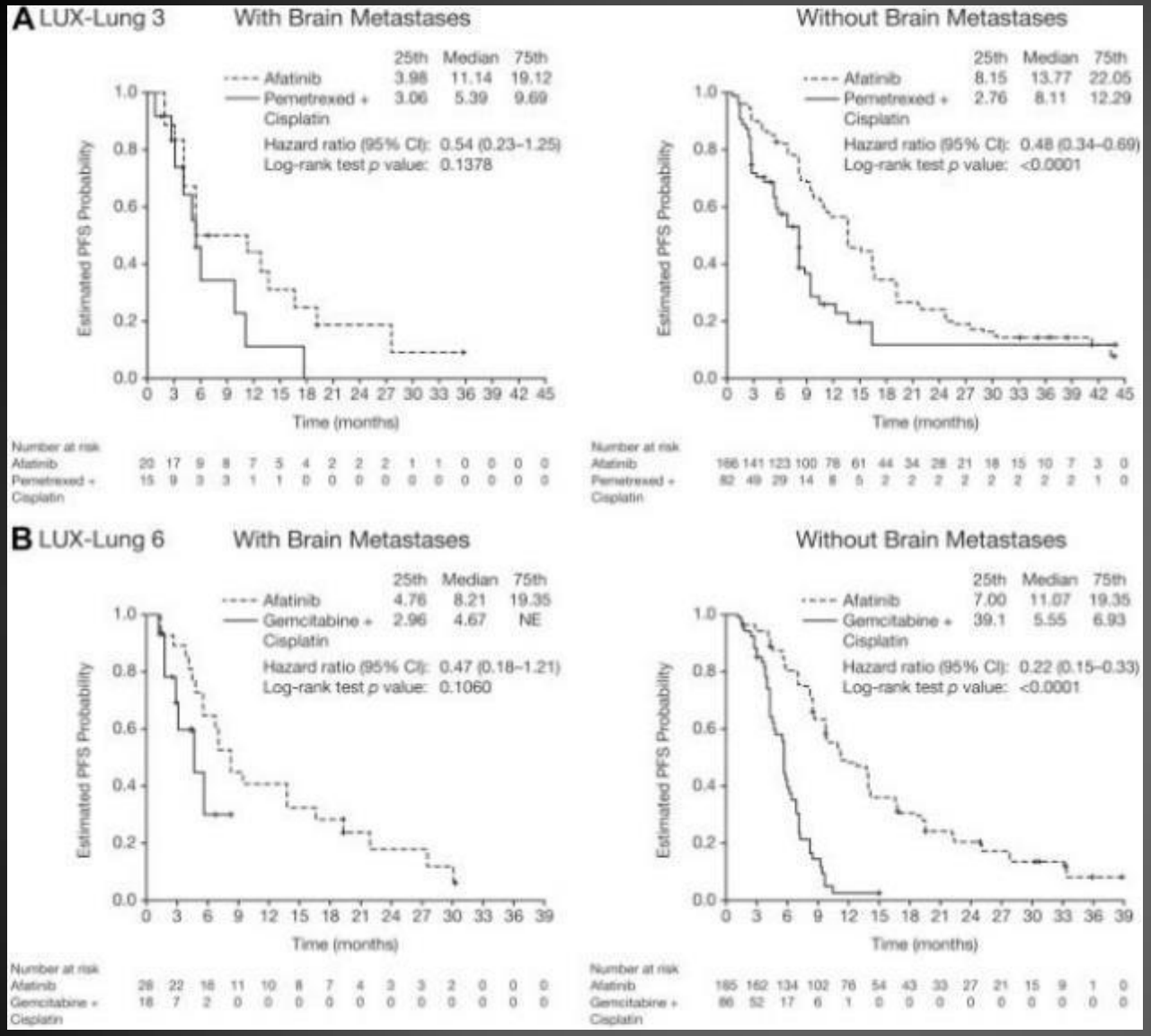
First-line afatanib in NSCLC EGFRmut+



BM 12% 13% 12% 16%

~13% had asymptomatic brain metastases at study entry of which 35% had had WBRT

Schuler M et al, JTO 2016



PFS benefit of afatinib similar in patients with/without BM

But NS p value for BM (small numbers?)

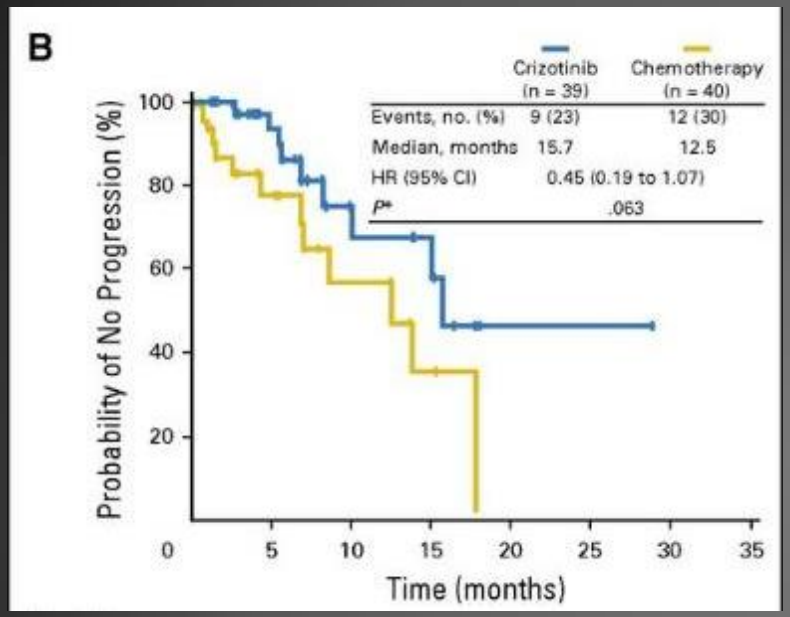
Longer time to CNS progression in afatinib arms

Benefit of afatinib appeared higher if prior WBRT

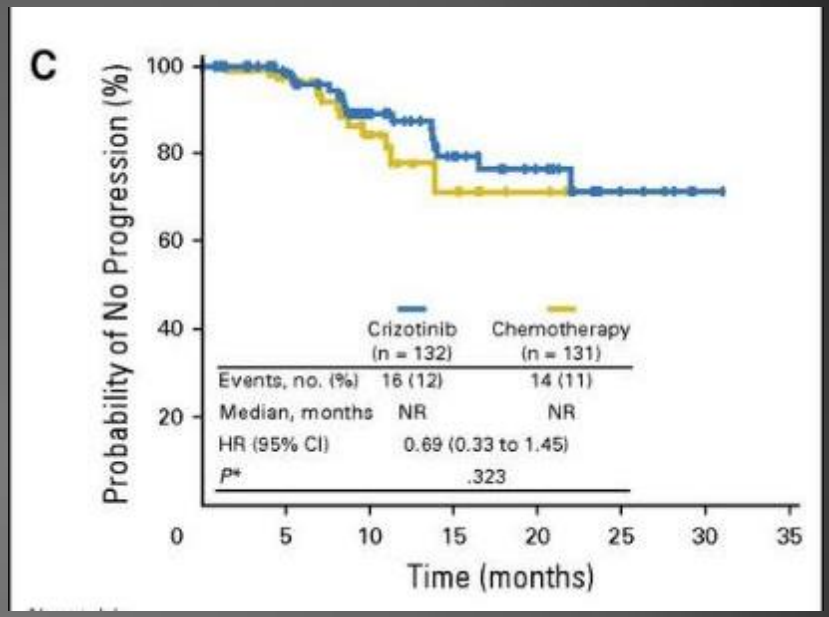
PFS 8.2 vs 4.7 months (p=.1) PFS 13.8 vs 8.1 months (p<.0001)

Schuler M et al, JTO 2016

Intracranial time-to-progression of crizotinib vs chemo in ALK+ NSCLC: PROFILE 1014



BM at baseline



No BM at baseline

- 23% had stable treated BM at baseline
- Of those BM patients, nonsignificant improvement in intracranial TTP with crizotinib (p=.064)
- Increase in brain as sole site of progression higher with crizotinib vs chemo
  - 24% vs 10% if no BM at baseline
  - 38% vs 23% if BM at baseline

Solomon BJ et al, JCO 2016

Examples of ongoing studies

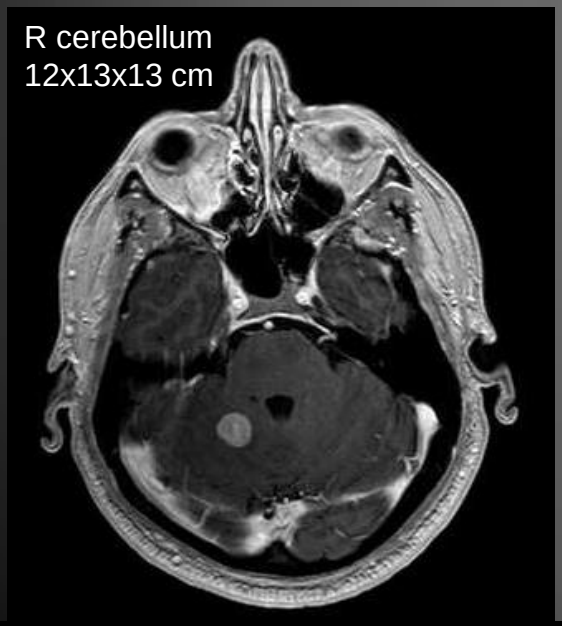
Study	Pt number + Eligibility	Primary Endpoint(s)
NCT01951469 China Randomized Ph II Gefitinib ± pem/cis	160 EGFR+, newly dx with ≥ 3 BM	Intracranial PFS at 3 yrs
NCT02556593 China Randomized Ph II IMRT + erlotinib vs WBRT	116 EGFR wild-type 4-10 BM,	Intracranial PFS at 2 yrs
NCT01887795 China Randomized Ph III WBRT ± Erlotinib	224 EGFR+, ≥ 2 BM	Intracranial control + time to neurologic progression at 13 months
NCT02314364 USA Ph II SBRT/SRS + TKI	30 ALK+/EGFR+/ROS1+, oligometastases extra/intracranial (1-4 brain)	Freq of distant failures at 1 yr
NCT02521051 USA Ph I/II Alectinib and Bev	43 ALK+, ≥ 1 untreated or progressive BM	Determining doses + Safety/tolerability
NCT02336451 USA Ph II Ceritinib	125 ALK+, brain±lepto	Overall RR at 24 wks

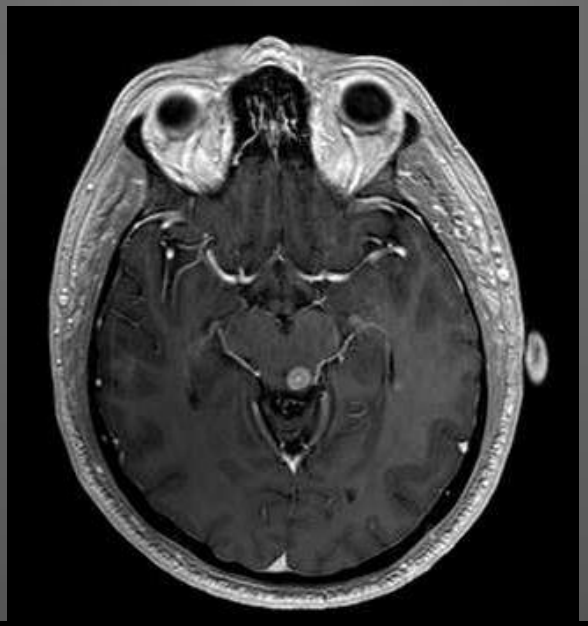
Current practice at University of Colorado for newly dx EGFRmut+/ALK+ NSCLC with brain metastases

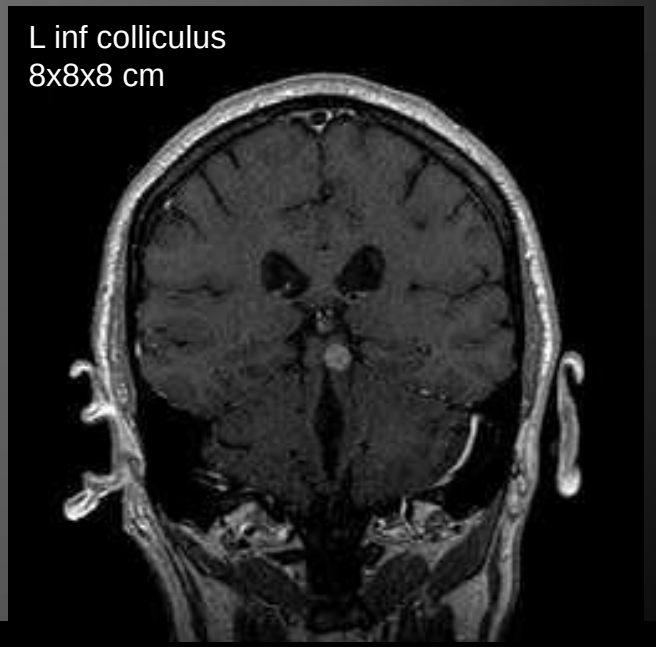
- SRS usually done if feasible/appropriate
- If SRS not feasible/appropriate, then TKI only
- SRS done as brain metastases progress or arise
- WBRT done in small percentage of patients

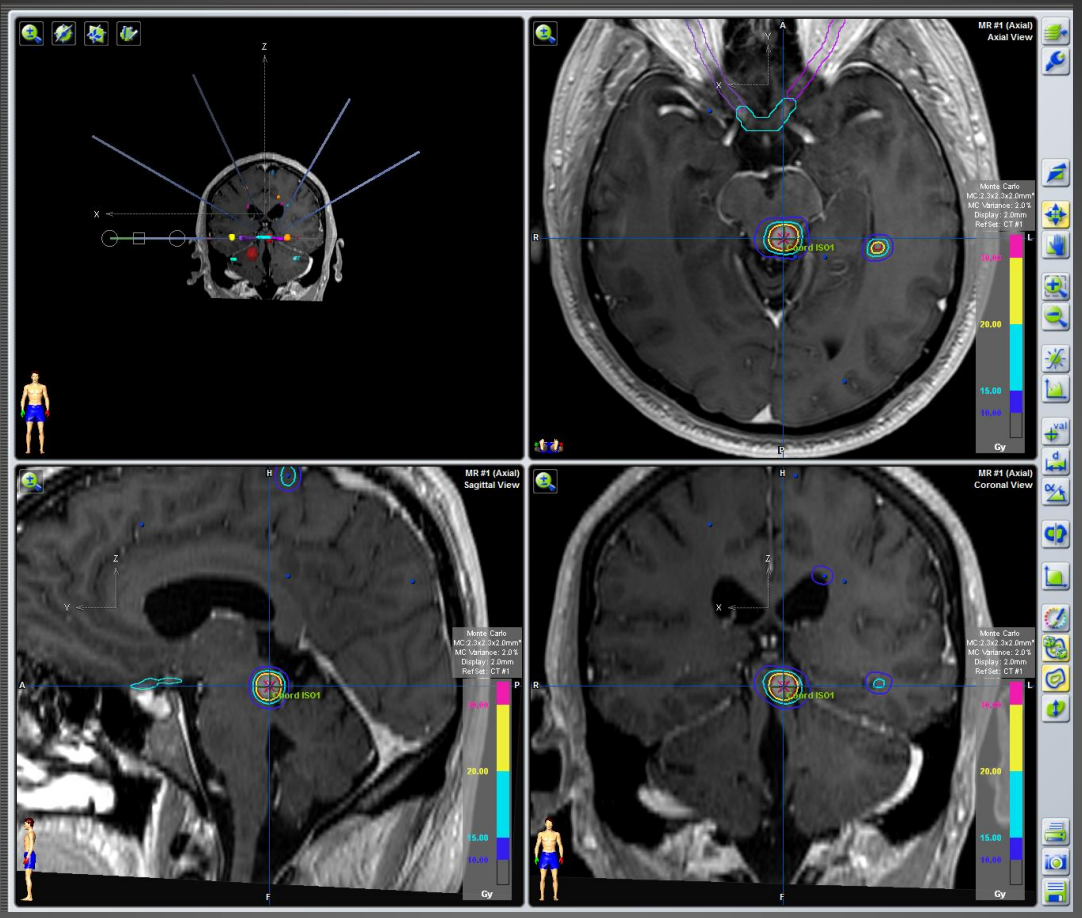
- 49 yr old M, never smoker, Stage IIIB adenoca ALK+April 2011 treated with definitive chemorads
- Jan 2014 recurrence L hilum, LLL lung, mesentery, L1, brain (9 lesions)

- Treatment to brain?
  - SRS
  - WBRT
  - SRS + WBRT



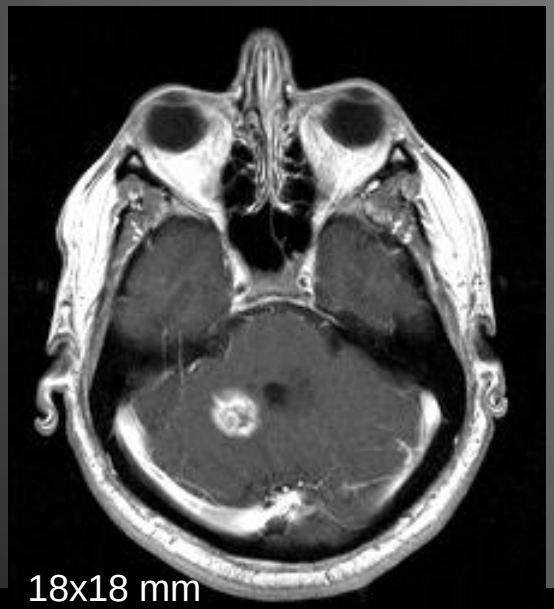






- Jan 2014 received 20 Gy to the 9 lesions with 5 isocenters
- Then started crizotinib.

- September 2014 ataxia, nystagmus, R sided paresis and R sided sensory changes
- MRI showed increase in many lesions in brain. No new lesions.
- Stable extracranial disease
- Mild improvement on steroids but symptoms recurred off steroids.
- What to do?
    - Referral to neurosurgery?
    - Steroids again?
    - Bevacizumab?



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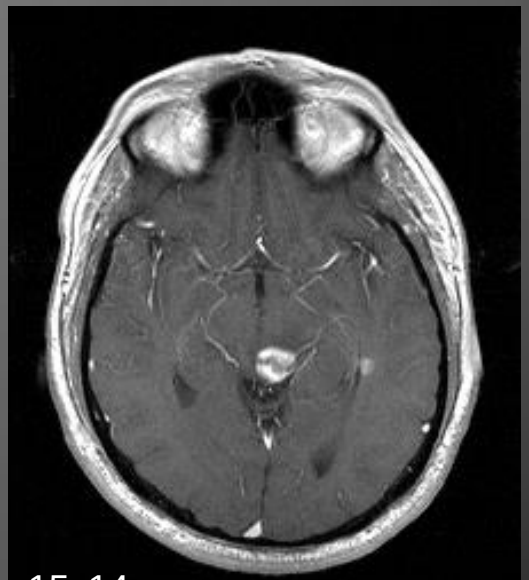

15x14 mm

- Received another course of steroids
- Started bevacizumab
- January 2016 2 new lesions, R parietal (enhancing) and L parietal (non-enhancing)
- Treatment?
  - Continued observation?
  - Change from crizotinib to another ALK inhibitor?
  - SRS to one or both lesions?
  - WBRT?